HFA-305

Date of Approval: JUL 2 1 2001

FREEDOM OF INFORMATION SUMMARY

NADA 141-230

PREVICOX Chewable Tablets
(firocoxib)

For the control of pain and inflammation associated with osteoarthritis in dogs.

Sponsored by:

Merial Limited
3239 Satellite Blvd., Bldg. 500
Duluth, GA 30096-4640

141-230

FOIS 1

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1. GENERAL INFORMATION:

a. File Number:	NADA 141-230
b. Sponsor:	Merial Ltd. 3239 Satellite Blvd., Bldg. 500 Duluth, GA 30096-4640 Drug Labeler Code: 050604
c. Established Name:	Firocoxib
d. Proprietary Name:	PREVICOX
e. Dosage Form:	Scored chewable tablets
f. How Supplied:	The product is available as 57 or 227 mg round half-scored tablets in 60 count bottles and 10-count and 30-count blister packages.
g. How Dispensed:	Rx
h. Amount of Active Ingredient:	Each tablet contains 57 mg or 227 mg firocoxib.
i. Route of Administration:	Oral
j. Species/Class:	Dogs
k. Recommended Dosage:	PREVICOX should be administered orally at a dose of 2.27 mg/lb (5.0 mg/kg) body weight once daily. The tablets are scored and dosage should be calculated in half-tablet increments.
l. Pharmacologic Category:	Non-steroidal anti-inflammatory drug (NSAID)
m. Indications:	PREVICOX is indicated for the control of pain and inflammation associated with osteoarthritis in dogs.

2. *EFFECTIVENESS:*

a. Dosage Characterization:

A once daily oral dose of 5.0 mg/kg (2.27 mg/lb) body weight was selected based on the results of studies conducted in an experimental arthritis model.

In dose titration studies, dogs received a placebo control, 2.5, 5.0 or 7.5 mg/kg firocoxib orally ten hours prior to induction of arthritis. Force plate gait analysis and clinical assessments were performed prior to treatment, and 14 and 18 hours after treatment.

There was significant improvement in peak vertical force for all three firocoxib-treated groups when compared to placebo control group at 14 hours and 18 hours after treatment ($p < 0.01$). Peak vertical force after treatment with 5.0 mg/kg was 87.7% of full weight bearing baseline at 14 hours after treatment and 84.9% of baseline at 18 hours after treatment. The corresponding figures for the untreated control group were 0.0% at 14 hours and 33.0% at 18 hours. The dose response to firocoxib reached a plateau between 2.5 and 5.0 mg/kg, inclusive. Five mg/kg given once daily was selected as the dose for further study.

A second study was conducted in an experimental arthritis model with once daily oral administration of 5.0 mg/kg firocoxib. Force plate gait analysis and clinical assessments were performed prior to treatment, and at three and seven hours after treatment during the period of peak lameness.

There was statistically significant improvement in peak vertical force and clinical lameness scores for firocoxib-treated dogs when compared to placebo control group at both three and seven hours after treatment ($p \leq 0.05$). Peak vertical force after treatment with 5.0 mg/kg was 72.0% of full weight bearing baseline at three hours after treatment and 99.3% of baseline at seven hours after treatment. The corresponding figures for the placebo control group were 40.6% at three hours and 69.6% at seven hours. Clinical lameness scores for firocoxib-treated dogs also improved significantly as compared to placebo control group at both three and seven hours after treatment ($p \leq 0.05$). This study further supported the choice of 5.0 mg/kg firocoxib.

b. Substantial Evidence:

(1) Field Studies (PR&D 00535 and PR&D 00538)

Titles: PR&D 00535: A Study to Demonstrate the Efficacy, Safety and Acceptability of a ML-1,785,713 Oral Tablet in Dogs for the Control of Pain and Inflammation Associated with Osteoarthritis Under Field Conditions

PR&D 00538: A Study to Assess the Efficacy, Safety and Acceptability of ML-1,785-713 Oral Tablet in Dogs for the Control of Pain and Inflammation Associated with Osteoarthritis Under Field Conditions

(a) Types of Studies: Active-controlled, Masked, Randomized Field Studies

(b) Investigators:

Investigators	Locations
Drs. Bert Shelley and Roger Sifferman	Springfield, MO
Dr. K.C. Brooks	Lodi, WI
Drs. Michael Conzemius and Wanda Gordon	Ames, IA
Drs. Jerry Case, Carla Case McCorvey and Melanie Bevere	Savannah, GA
Dr. James Schuessler	St. Louis, MO

(c) General Design:

1 Purpose: The objective of these studies was to demonstrate, under field use conditions, the effectiveness, safety and acceptability of firocoxib for the control of pain and inflammation associated with osteoarthritis in dogs.

2 Test Animals: Two hundred forty-nine dogs of various breeds were enrolled. The dogs ranged in age from 11 months to 20 years and weighed from 6.3 to 175 lbs. Two hundred forty dogs were used in the effectiveness evaluation.

3 Active Control: ETOGESIC (etodolac), 150 mg or 300 mg tablets

4 Diagnosis: Enrolled dogs were diagnosed with osteoarthritis via recent radiographic evidence of degenerative or bony changes. The dogs also had lameness scores of at least 2 (on a scale of 0 = no lameness to 4 = non-weight bearing lameness) at a walk or trot, or a combined score of at least 3 for lameness at a walk or trot, plus pain on palpation, swelling, or range of motion (on a scale for each variable of 0 = not present to 3 = severe).

5 Dose Form: Final market formulation of PREVICOX Chewable Tablets for Dogs, either 57 mg or 227 mg tablets.

6 Route of Administration: Oral

7 Dosages used: 5.0 mg/kg body weight of firocoxib, administered orally once daily; 10-15 mg/kg body weight of the active control, administered orally once daily.

8 Treatment Duration: 30 days

9 Variables Measured: For all dogs enrolled in the studies, physical examinations and lameness evaluations were conducted by the Investigator at the initial visit (Day –6 to Day 0), at the midpoint (approximately Day 14), and at the study's end (Day 29 +/- 3 days). Hematology and serum chemistry were evaluated prior to enrollment and at Day 29 +/- 3 days (only for dogs in PR&D 00535). The primary variable of effectiveness was the percentage of subjective improvement at the study end point. Improvement (treatment success) was defined as one of the following:

a. Reduction of at least 1 grade in lameness score at a walk or trot,

and/or

b. A combined reduction of at least 2 grades in scores for pain on palpation or manipulation, range of joint motion, and joint swelling

Overall lameness, pain on palpation or manipulation, range of motion, and joint swelling were observed at the three scheduled times and scored as follows:

Overall Lameness Scoring (scored at a walk and a trot)
0 = No lameness
1 = Mild lameness (dog touched toe to floor on all strides)
2 = Moderate lameness (dog touched toe to floor on all strides)
3 = Severe lameness (dog touched toe to floor on at least 50% of strides)
4 = Non-weight bearing lameness (dog touched toe to floor on less than 50% of strides)

Pain on Palpation/Manipulation (most severely affected limb)
0 = No pain or not applicable
1 = Slightly painful (scarcely withdrew limb)
2 = Moderately painful (definitely withdrew limb)
3 = Severely painful (prominently withdrew limb)

Range of Motion (most severely affected limb)
0 = Normal range of motion
1 = Slightly reduced (less than 25% reduction in range)
2 = Moderately reduced (25% to 50% reduction in range)
3 = Severely reduced (greater than 50% reduction in range)

Joint Swelling (most severely affected limb)
0 = No swelling or not applicable
1 = Mild swelling (fibrosis or mild, palpable fluid distension)
2 = Moderate swelling (obvious, palpable fluctuant fluid distension)
3 = Severe swelling (pronounced, palpable fluctuant fluid distension)

Owners subjectively scored improvement from the initial visit on approximately Days 7, 14, 21 and 29. General health observations were also recorded daily by the owners. At the end of the study, owners assessed whether the tablet was convenient to administer, and if the tablet was palatable to the dog. Scoring of improvement was as follows:

Improvement
0 = Greatly improved from initial visit
1 = Moderately improved from initial visit
2 = Mildly improved from initial visit
3 = No improvement from initial visit

For the dogs enrolled in study PR&D 00535, peak vertical force during trotting was assessed by force plate gait analysis of the most severely affected limb at baseline (Day –2 to Day 0) and at study's end (approximately Day 29).

(d) Results:
Two hundred and forty nine dogs were enrolled in the studies. Two hundred forty dogs were evaluated for effectiveness. Safety data were collected on all dogs receiving treatment for any period.

Treatment with 5.0 mg/kg firocoxib orally once daily resulted in overall clinical improvement that was comparable to the active control at both study midpoint (Day 14) and endpoint (Day 29). Both treatment groups showed improvement from the initial visit. The results are summarized in Table 1.

Table 1. Veterinary Clinical and Non-Inferiority Evaluation

Group	**Percentage of Dogs with Overall Veterinary Clinical Improvement**	
Treatment	**Day 14 (Visit 2)**	**Day 29 (Visit 3)**
Firocoxib	80.2% (97/121*)	87.6% (106/121)
Active Control	78.8% (93/118)	83.1% (98/118)
Test Article-Active Control (Lower Confidence Bound)	1.4% (-7.4%)	3.8% (-3.9%)
Is non-inferiority demonstrated? (margin of difference is 15%)	Yes	Yes

*One case had missing data for Visit 2 since the examination was not performed within the time frame specified in the protocol.

Table 2 summarizes the percentage of dogs that showed improvement in the two components that formed the veterinary clinical evaluation. The first

component evaluated "lameness at a trot" and "lameness at a walk." In order for an animal to be classified as "improved" in the lameness component, it had to show a decrease of at least one grade on at least one of the two lameness variables. The second component of the clinical improvement evaluation evaluated "pain on palpation or manipulation," "range of motion," and "joint swelling." In order for an animal to be classified as "improved" in this component, it had to show an improvement of at least two grades in any of these three variables taken together. This could be demonstrated by either an improvement of two grades on one of the variables, or an improvement of one grade on two of the variables.

Table 2. Percentage of Dogs Showing Improvement in Veterinary Clinical Evaluation

	Percentage of Dogs that Showed Improvement	
Group	**Lameness at a walk and lameness at a trot**	**Pain on palpation, range of motion, and joint swelling**
Visit 2		
Firocoxib	76.0% (92/121*)	55.4% (67/121)
Active Control	76.3% (90/118)	43.2% (51/118)
Visit 3		
Firocoxib	82.0% (100/122*)	63.9% (78/122)
Active Control	78.8% (93/118)	47.5% (56/118)

*One case had missing data for Visit 2 since the examination was not performed within the time frame specified in the protocol.

Of the 249 dogs enrolled in the study, 172 dogs underwent force plate measurement of peak vertical force in gait. Of these, 164 dogs were included in the analysis. Eight dogs were excluded from the analysis for non-treatment-related reasons. Increased weight bearing on the affected limb, as measured by change in peak vertical force (Newtons/kilogram, N/kg) between the initial visit and study end, was comparable for firocoxib (0.15 N/kg; n = 87) and active control (0.20 N/kg; n = 80). The results are summarized in Table 3.

Table 3. Improvement in Peak Vertical Force on Day 29 (Visit 3)

Group	Percentage of Dogs with Improvement[1]
Firocoxib	14.1% (12/85)
Active Control	12.7% (10/79)
Test Article-Active Control (Lower Confidence Bound)	1.6% (-7.8%)
Is non-inferiority demonstrated? (Margin of difference is -15%)	Yes

[1]The criterion for classifying a dog as "improved" was an increase of at least 0.74 N/kg (Newtons/kg) in the dog's mean peak vertical force on Day 29 compared with its mean peak vertical force at baseline. The criterion was calculated as two times the pooled within-dog standard deviation of 0.37 N/kg.

Based on once weekly owner evaluations, improvement between firocoxib and the active control was comparable at all time points (Days 7, 14, 21, and 29). The scoring scale and values for each response at each evaluation are summarized in Table 4. Both firocoxib and the active control were rated palatable (68.5% and 53.7%, respectively) and convenient to administer (97.2% and 87.2%, respectively) by owners.

Table 4. Results of Owner Evaluation of Improvement*

Time	Scoring	Firocoxib	Active Control
Day 7	0 = greatly improved	19.3% (23/119)	6.8% (8/116)
	1 = moderately improved	21.0% (25/119)	18.1% (21/116)
	2 = mildly improved	39.5% (47/119)	48.3% (56/116)
	3 = no improvement	20.2% (24/119)	26.7% (31/116)
Day 14	0 = greatly improved	20.8% (25/120)	8.5% (10/118)
	1 = moderately improved	33.3% (40/120)	31.4% (37/118)
	2 = mildly improved	31.7% (38/120)	38.1% (45/118)
	3 = no improvement	14.2% (17/120)	22.0% (26/118)
Day 21	0 = greatly improved	28.3% (34/120)	10.2% (12/118)
	1 = moderately improved	33.3% (40/120)	35.6% (42/118)
	2 = mildly improved	25.8% (31/120)	34.7% (41/118)
	3 = no improvement	12.5% (15/120)	19.5% (23/118)
Day 29	0 = greatly improved	32.8% (39/119)	16.9% (20/118)
	1 = moderately improved	31.1% (37/119)	32.2% (38/118)
	2 = mildly improved	23.5% (28/119)	28.8% (34/118)
	3 = no improvement	12.6% (15/119)	22.0% (26/118)

*Not all dogs were evaluated at each time point by the owners.

Minimal clinicopathologic changes were not treatment-related nor associated with clinical disease. The number of dogs with possible gastrointestinal (GI) tract-associated blood and protein loss was similar in both treatment groups (two firocoxib and three etodolac-treated dogs). These dogs had a minimum of three of the following findings: decreased red blood cell count, decreased hematocrit, increased or decreased mean corpuscular volume, decreased albumin, decreased globulins, and decreased total protein. One firocoxib-treated dog had a two-fold increase in neutrophils. One firocoxib-treated dog also had a two-fold increase in baseline BUN and creatinine (creatinine was 1.5 times normal reference range values). Hypocalcemia was noted in one firocoxib-treated dog and one etodolac-treated dog (Day 29 values were below normal reference range values for both dogs).

(e) Statistical Analysis:

The primary effectiveness variable was the incidence of veterinary clinical improvement at study end. Comparison of treatments for incidence of clinical improvement was performed as a non-inferiority comparison, with a one-sided lower 95% confidence limit. Improvement at study midpoint was also analyzed. Improvement was defined as: 1) Reduction of at least one grade in lameness score at a walk or a trot, and/or 2) Combined reduction of at least two grades in scores for pain on palpation or manipulation, range of motion, and joint swelling. Improvement was then assigned a value of "1" if improved or "0" if not improved.

Secondary effectiveness variables included veterinary scores for lameness at a walk or a trot, pain on palpation or manipulation, range of motion, and joint swelling, and the owner's assessment of improvement.

Analysis of peak vertical force was made based on the mean of valid observations on the designated limb. A dog was classified as "improved" if its peak vertical force increased from its baseline by at least two times the pooled within-dog standard deviation, obtained from repeated force plate trials. A non-inferiority evaluation was used to compare the incidence of improvement of firocoxib-treated dogs with active control-treated dogs, using a margin of –15%, as previously described for the overall clinical evaluation of improvement. The incidence of overall clinical improvement with firocoxib was within the margin of difference established for the non-inferiority comparison with the active control.

(f) Conclusions:

In field studies, firocoxib was shown to be safe and effective when administered at 5.0 mg/kg orally once daily for the control of pain and inflammation associated with osteoarthritis in dogs. Owners found chewable firocoxib tablets both convenient to administer (97.2%) and palatable (68.5%) to their dogs.

(g) Adverse Reactions:

Adverse reactions were reported in both treatment groups during the studies. Vomiting and decreased food consumption were the most common clinical adverse events seen in both the firocoxib and active control groups.

Table 5. Adverse Reactions Seen During the U.S. Field Studies

Adverse Reactions*	Firocoxib n=128**	Active Control n=121**
Vomiting	5	8
Decreased food consumption/Anorexia	3	3
Pain	2	1
Diarrhea	1	10
Lethargy	1	3
Somnolence	1	1
Hyperactivity	1	0
Melena	0	3
Stomatitis	0	1
Icterus	0	1
Constipation	0	1
Drooling	0	1
Alopecia	0	1

*Dogs may have experienced more than one adverse event during the study.
**"n" represents the total number of dogs in the treatment group.

3. *TARGET ANIMAL SAFETY*

a. PR&D 0078601: A Study to Evaluate the Safety of Firocoxib Administered to Dogs in an Oral Chewable Tablet Formulation at 1, 3, and 5X the Recommended Dose

(1) Type of Study: Laboratory Study

(2) Investigator: Marlene D. Drag, DVM, MS, DACLAM
Merial-Missouri Research Center
Fulton, MO

(3) General Design:
(a) Purpose: To determine the safety of firocoxib administered to dogs orally once daily at 1, 3, and 5X the recommended dose of 5 mg/kg for six months.
(b) Test Animals: Thirty-two Beagle dogs (16 male and 16 female, ranging in weight from 7.70 to 14.75 kg, and in age from 7 to 10.9 months) were randomly assigned to four treatment groups (eight dogs per group).
(c) Control: Control dogs were not medicated.
(d) Dose Form: Scored tablets containing either 57 mg or 227 mg of firocoxib in the final market formulation
(e) Route of administration: Oral
(f) Dosage: Table 6 lists the treatment groups and the dose used for each:

Table 6. Treatment Groups

Treatment Groups	Dose, mg/kg	Number and Sex Of Animals
1	0	4 male and 4 female
2	5 mg/kg (1X)	4 male and 4 female
3	15 mg/kg (3X)	4 male and 4 female
4	25 mg/kg (5X)	4 male and 4 female

(g) Duration of Treatment: Six months

(h) Variables measured: Physical examination, general and post-dosing observations, food consumption, palatability, body weight, clinical chemistry, coagulation, hematology, plasma levels of firocoxib, urinalysis, gastric endoscopy, and gross (all animals) and histopathologic evaluation (controls and 5X animals)

(4) Results:

One dog in the 3X dose group was diagnosed with juvenile polyarteritis of unknown etiology after exhibiting episodes of vomiting and diarrhea, lethargy, pain, anorexia, ataxia, and proprioceptive deficits. Other clinical signs in this dog included elevated white blood cell counts, decreased and then increased platelet counts, decreased albumin levels, increased bleeding times, and elevated liver enzymes.

Decreased appetite/anorexia, vomiting, and diarrhea were seen in all dogs in all dose groups, including unmedicated controls, although vomiting and diarrhea were seen more often in dogs in the 5X dose group.

On histopathologic examination, a mild ileal ulcer and a focal hemorrhage in the heart was found in one 5X dog. This dog also had a transient elevation in white blood cell count and platelet count, and a transient decreased serum albumin, which returned to normal by study completion. One control and three 5X dogs had focal areas of inflammation in the pylorus or small intestine. Thalamic vacuolization was seen in two 5X group dogs, one 3X dog, and in two control dogs. The lesions were more severe in the 5X dogs. External thalamic capsular vacuolization was also seen in one control dog and in one 5X dog.

Sporadic incidences of increased white blood cell counts and decreased albumin were seen in all dose groups, including controls, but were seen at a greater frequency in the 3X and 5X groups. Mean ALP was within the normal reference range for all groups, but was statistically significantly greater in the 3X ($p = 0.0269$) and 5X ($p = 0.0816$) dose groups than in the control group.

Analysis of plasma levels of firocoxib indicated that the drug was absorbed and systemically available at all doses. Plasma concentrations increased with dose, and were approximately proportional to dose over the dose range.

(5) Conclusions: This study demonstrated the safety of long-term administration of firocoxib in dogs over seven months of age. Dogs administered firocoxib once daily at the recommended dose for 180 days showed no clinically significant adverse events. At higher doses, transient hypoalbuminemia, leukocytosis, and elevations in ALP were reported. On histopathologic examination, a mild ileal ulcer was found in one 5X dog.

b. PR&D 0054101: A Safety Study to Evaluate the Toxicity of Firocoxib Oral Chewable Tablet Formulation Administered to Dogs at 1, 3, and 5X the Maximum Label Recommended Dose

(1) Type of Study: Laboratory Study

(2) Investigator: Sarah Nolan Smith, BSc, CBiol, MIBiol
Covance Laboratories Europe, Ltd.
North Yorkshire, HG3 1PY, United Kingdom

(3) General Design:
(a) Purpose: To determine the safety of firocoxib administered to dogs orally once daily at 1, 3, and 5X the recommended dose of 5 mg/kg for six months.
(b) Test animals: Thirty Beagle puppies (15 male and 15 female, ranging in age from 10-13 weeks at study start, and weighing 2.59-4.57 kg) were randomly assigned to five treatment groups (3 dogs per sex per treatment group). Table 7 lists the treatment groups, their doses, and the number of animals per group. Group E was intended to be a recovery group to examine the reversibility of lesions following 180 days of treatment and an additional 60 days without treatment.

Table 7. Treatment Groups

Treatment Group*	Dose (mg/kg)	Number and Sex of Animals
A	0	3 males and 3 females
B	5 mg/kg (1X)	3 males and 3 females
C	15 mg/kg (3X)	3 males and 3 females
D	25 mg/kg (5X)	3 males and 3 females
E	25 mg/kg (5X)	3 males and 3 females

(c) Control: Control puppies were not medicated.
(d) Dose Form: Scored chewable tablets containing 57 mg or 227 mg firocoxib (final market formulation)
(e) Route of administration: Oral
(f) Dosage: Each puppy's weight was multiplied by the desired dose multiple (for example 1 x bw, 3 x bw, 5 x bw where bw is the animal's body weight). Each dog was then dosed according to Table 8.

Table 8. Dosage Administration Table

CALCULATED WEIGHT MULTIPLE	TABLET SIZE/ ACTUAL DOSE
2.3-5.7 kg (5-12.5 lb)	½ tablet 57 mg (12.3-5 mg/kg)
5.8-11.3 kg (12.6-25 lb)	(1) 57 mg tablet (9.8-5 mg/kg)
11.4-22.7 kg (25.1-50 lb)	½ tablet 227 mg (9.9-5mg/kg)
22.8-45.4 kg (50.1-100 lb)	(1) 227 mg tablet (9.9-5 mg/kg)
Over 45.4 kg (over 100 lb)	Appropriate tablet combination

(g) Test duration: One hundred and eighty days (six months)
(h) Variables measured: Body weight, physical examination, post-dosing observations, plasma firocoxib levels, clinical chemistry and hematology, buccal mucosal bleeding times, urinalysis, gastric endoscopy, and gross and histopathologic evaluation

(4) Results: Four moribund puppies (one of six treated at 3X on Day 63, and three of twelve treated at 5X the indicated dose on Days 38, 78, and 79) were euthanized because of anorexia, weight loss, depression, and in one dog, vomiting. One puppy treated with firocoxib at 5X died on Day 82. The 3X puppy that was euthanized also had a decreased serum albumin. Two of the five animals that died or were euthanized had elevations in liver enzymes; these two animals were in the 5X dose group. One puppy had ingested a rope toy, which may have contributed to its demise.

When examined at necropsy and by histopathology, these five puppies all had moderate to severe periportal hepatic fatty change, two had duodenal ulceration, and two of the puppies also had pancreatic edema. One of these puppies had renal casts and one had renal hyaline droplets, although no corresponding lesions were seen on histopathology.

The remaining four 5X puppies from dose group D and two control puppies, all clinically normal, were euthanized to serve as comparisons to the ill animals. Two of these 5X puppies had periportal hepatic fatty change. One 5X puppy had focal nephropathy.

On average, the puppies in the 3X and 5X dose groups did not gain as much weight as controls. Rate of weight gain was measured (instead of weight loss) because these were young growing dogs.

On day 83 of the study, dosing was discontinued for all puppies in both 5X dose groups. The four surviving puppies from 5X dose group E continued unmedicated for the remainder of the study (14 weeks). They had no significant lesions at necropsy at 180 days.

At 5 mg/kg, three out of six puppies had minimal periportal hepatic fatty change at necropsy, following 180 days of treatment. These animals showed no antemortem clinical signs or liver enzyme elevations. In the 3X dose group, three of the five surviving puppies had minimal periportal hepatic fatty change, one had pancreatitis, one had cystitis, and one had caecitis. Thalamic vacuolization was seen in three of six puppies in the 3X group and five of twelve puppies in the 5X groups. Diarrhea was seen in all dose groups.

(5) Conclusions: At 5 mg/kg, firocoxib treatment was associated with subclinical periportal hepatic fatty change in puppies less than seven months of age. At higher dose groups in this age dog, duodenal ulceration, hepatic fatty change, decreased weight gain, and decreased serum albumin were observed. One of twelve 5X puppies died and one of six 3X and three of twelve 5X puppies developed serious adverse reactions such as vomiting and depression, requiring euthanasia. The severity of the adverse reactions at the 3X and 5X doses, and the subclinical periportal hepatic fatty change in three of six puppies treated at the indicated dose, suggest that the drug may not be safe in young dogs. Furthermore, thalamic vacuolization was seen in three of six puppies in the 3X group and five of twelve puppies in the 5X groups. The clinical significance of this change is unknown.

c. PR&D 0053301: A Safety Study to Evaluate the Tolerance (10X) of Dogs to Firocoxib Chewable Tablet

(1) Type of Study: Laboratory Study

(2) Investigator: Marlene D. Drag, DVM, MS, DACLAM
Merial-Missouri Research Center
Fulton, MO

(3) General Design
(a) Purpose: To evaluate the safety of firocoxib in dogs at ten times the indicated dose for 22 days.
(b) Test Animals: Six Beagle dogs, three males and three females, ranging in age from 11-14 months old, weighing 10.6 to 13.25 kg body weight
(c) Control: Control animals were not medicated.

(d) Dose Form: Firocoxib in 57 mg and 227 mg scored tablet sizes (final market formulation)
(e) Route of Administration: Oral
(f) Dosage: The treatment groups, doses used, and numbers of animals per group are described in Table 9.

Table 9. Treatment Groups

Treatment Group	Dose mg/kg	Number and Sex of Animals
1	0	2 (1 male and 1 female)
2	10X (≥50 mg/kg)	4 (2 male and 2 female)

(g) Test Duration: Twenty-two days
(h) Variables measured: Body weight, food consumption, physical examination, post-dosing observations, hematology and clinical chemistry, buccal mucosal bleeding times, urinalysis, gastric endoscopy, and gross and histopathologic evaluation.

(4) Results: All dogs survived to the end of the study. Three of four treated dogs developed small intestinal erosion or ulceration. Treated dogs that developed small intestinal erosion or ulceration had a higher incidence of vomiting, diarrhea, and decreased food consumption/anorexia than control dogs.

One of these treated dogs developed a severe duodenal ulceration, with centrolobular hepatic fatty change and associated vomiting, diarrhea, anorexia, weight loss, ketonuria, and elevations in AST and ALT. All four treated dogs exhibited progressively decreasing serum albumin that, with the exception of one dog that developed hypoalbuminemia, remained within normal range. Mild weight loss also occurred in the treated group. One control dog and three treated dogs exhibited transient increases in ALP that remained within normal range.

(5) Conclusions: Firocoxib administered at ten times the recommended dose (50 mg/kg) for 22 days resulted in small intestinal erosion or ulceration, decreased food consumption/anorexia, mild weight loss, sporadic vomiting and diarrhea, and decreased serum albumin in three of four treated animals. Increased in liver enzymes and ketonuria were observed in treated dogs. Hepatic fatty change was confirmed in one dog.

4. HUMAN FOOD SAFETY

This drug is intended for use in dogs which are non-food animals. Because this new animal drug is not intended for use in food-producing animals, data on human food safety pertaining to drug residues in food were not required for approval of this NADA.

Human Warnings are provided on the label as follows: "Warnings: Not for use in humans. Keep this and all medications out of reach of children. Consult a physician in case of accidental ingestion by humans. **For use in dogs only.**"

5. *AGENCY CONCLUSIONS*

The data submitted in support of this NADA comply with the requirements of Section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR Part 514 of the implementing regulations. The data demonstrate that PREVICOX (firocoxib) Chewable Tablets, when used under the labeled conditions of use are safe and effective for the control of pain and inflammation associated with osteoarthritis in dogs.

PREVICOX (firocoxib) Chewable Tablets are restricted to use by or on the order of a licensed veterinarian because professional veterinary expertise is needed to diagnose canine osteoarthritis and to monitor response to treatment.

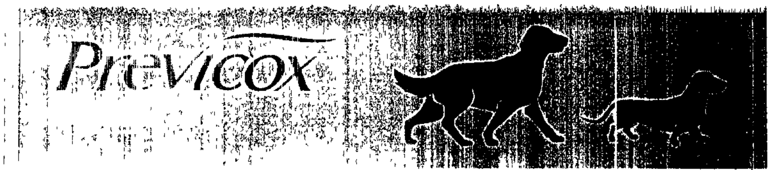
Under Section 512(c)(2)(F)(i) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for FIVE years of marketing exclusivity beginning on the date of approval because no active ingredient of the new animal drug has previously been approved.

U.S. Patent Number	Date of Expiration
5,981,576	October 9, 2016
6,541,646	October 8, 2019
6,677,373	October 8, 2019

6. *ATTACHMENTS*

Facsimile labeling is attached as indicated below:

a. Package insert for both 57 mg and 227 mg tablet sizes
b. Client Information Sheet for PREVICOX Chewable Tablets, 57 mg and 227 mg tablet sizes
c. Bottle label for 60 count bottle for both 57 mg and 227 mg tablet sizes
d. 30 count blister backing label for both 57 and 227 mg tablet sizes
e. Carton labels for 30 count blister packages for both 57 and 227 mg tablet sizes
f. 10 count blister backing label for both 57 and 227 mg tablet sizes
g. Carton labels for 10 count blister packages for both 57 and 227 mg tablet sizes
h. Display trays for 10 count and 30 count blister packages for both 57 and 227 mg tablet sizes
i. Shipping label for 60 count bottles of 57 and 227 mg tablet sizes
j. Shipping label for 30 count blister cartons of 57 and 227 mg tablet sizes
k. Shipping label for 10 count blister cartons of 57 and 227 mg tablet sizes



[illegible]

Contraindications [illegible]

Warnings [illegible] ... accidental ingestion ...

For ... mg/kg) in puppies less than ... months of age ... serious adverse reactions including ...

All dogs ... physical examination ... Initiation of NSAID ... laboratory testing ... hematological ... is recommended prior ... during administration of an NSAID. ***Owners should be advised to observe for signs of potential drug toxicity (see Adverse Reactions and Animal Safety) and be given a Client Information Sheet about PREVICOX™ Chewable Tablets.***

For technical assistance ... adverse events, call 1-866-638-2226

Precautions This product ... dose accurately in dogs less than ... pounds in body weight.

Consider appropriate washout times when switching from one NSAID to another.

As a class, cyclooxygenase inhibitory NSAIDs may be associated with renal and gastrointestinal toxicity. Sensitivity to drug associated adverse events varies with the individual patient. Patients at greatest risk for renal toxicity are those that are dehydrated, on concomitant diuretic therapy, or those with existing renal, cardiovascular, and/or hepatic dysfunction. Concurrent administration of potentially nephrotoxic drugs should be carefully approached. NSAIDs may inhibit the prostaglandins that maintain normal homeostatic function. Such anti-prostaglandin effects may result in clinically significant disease in patients with underlying or pre-existing disease that has not been previously diagnosed. Since many NSAIDs possess the potential to produce gastrointestinal ulcerations, concomitant use with other anti-inflammatory drugs, such as NSAIDs or corticosteroids, should be avoided or closely monitored. The concomitant use of protein bound drugs with PREVICOX™ Chewable Tablets has not been studied in dogs. Commonly used protein bound drugs include cardiac, anticonvulsant and behavioral medications. The influence of concomitant drugs that may inhibit the metabolism of PREVICOX™ Chewable Tablets has not been evaluated. Drug compatibility should be monitored in patients requiring adjunctive therapy.

The safe use of PREVICOX™ Chewable Tablets in pregnant, lactating or breeding dogs has not been evaluated.

Adverse Reactions In controlled field studies, 128 dogs (ages 11 months to 15 years) were evaluated for safety when given PREVICOX™ Chewable Tablets at a dose of 5.0 mg/kg orally once daily for 30 days. The following adverse reactions were observed. Dogs may have experienced more than one of the observed adverse reactions during the study.

Adverse Reactions Seen in U.S. Field Studies

Adverse Reactions	*Previcox™ n=128*	*Active Control n=121*
Vomiting	5	8
Diarrhea	1	10
Decreased Appetite or Anorexia	3	3
Lethargy	1	3
Pain	2	·
Somnolence	1	1
Hyperactivity	1	0

PREVICOX™ (firocoxib) Chewable Tablets were safely used during field studies concomitantly with other therapies, including vaccines, anthelmintics and antibiotics.

Clinical Pharmacology Mode of action: PREVICOX™ (firocoxib) is a cyclooxygenase-inhibiting (coxib) class, non-narcotic, non-steroidal anti-inflammatory drug (NSAID) with anti-inflammatory and analgesic properties. There are two main cyclooxygenase enzymes, COX-1 and COX-2, and a newly discovered third enzyme, COX-3, which has yet to be fully characterized.[1] Cyclooxygenase-1 (COX-1) is the enzyme responsible for facilitating constitutive physiologic processes, e.g. platelet aggregation, gastric mucosal protection, and renal perfusion.[2] It also is constitutively expressed in the brain, spinal cord, and reproductive tract.[3] Cyclooxygenase-2 (COX-2) is responsible for the synthesis of inflammatory mediators, but it is also constitutively expressed in the brain, spinal cord and kidneys.[4,5,6] Cyclooxygenase-3 (COX-3) is also constitutively expressed in the canine and human brain and also the human heart.[7] Results from *in vitro* studies showed firocoxib to be highly selective for the COX-2 enzyme ... comparable to those ... However, the clinical ... established.

Effectiveness Two hundred and ... dogs of various breeds, ranging in age from ... months to ... years and weighing ... to 175 lbs, were randomly ... PREVICOX™ or an active control drug in two field studies. Dogs ... lameness, pain on manipulation, range of motion, joint ... and overall improvement ... noninferiority evaluation of PREVICOX™ ... with the active control ... percent of the owners rated ... dogs as improved ... percent of dogs treated with PREVICOX™ were also judged improved by the veterinarians. Dogs treated with PREVICOX™ showed a level of improvement in veterinarian-assessed lameness, pain on palpation, range of motion, and owner-assessed improvement that was comparable to the active control. The level of improvement in PREVICOX™ treated dogs in limb weight bearing on the force plate gait analysis assessment was comparable to the active control.

Palatability PREVICOX™ Chewable Tablets were rated both convenient to ... 2% and palatable to the dog (68.5% ... owners in multi-center field studies involving client owned dogs of various breeds and sizes.

Animal Safety In a target animal safety study, firocoxib was administered orally to healthy adult Beagle dogs (eight dogs per group) at 5, 15, and 25 mg/kg (1, 3, and 5 times the recommended total daily dose) for 180 days. At the indicated dose of 5 mg/kg, there were no treatment-related adverse events. Decreased appetite, vomiting, and diarrhea were seen in dogs in all dose groups, including unmedicated controls, although vomiting and diarrhea were seen more often in dogs in the 5X dose group. One dog in the 3X dose group was diagnosed with juvenile polyarteritis of unknown etiology after exhibiting recurrent episodes of vomiting and diarrhea, lethargy, pain, anorexia, ataxia, proprioceptive deficits, decreased albumin levels, decreased and then elevated platelet counts, increased bleeding times, and elevated liver enzymes. On histopathologic examination, a mild ileal ulcer was found in one 5X dog. This dog also had a decreased serum albumin which returned to normal by study completion. One control and three 5X dogs had focal areas of inflammation in the pylorus or small intestine. Vacuolization without inflammatory cell infiltrates was noted in the thalamic region of the brain in three control, one 3X, and three 5X dogs. Mean ALP was within the normal range for all groups but was greater in the 3X and 5X dose groups than in the control group. Transient decreases in serum albumin were seen in multiple animals in the 3X and 5X dose groups, and in one control animal.

In a separate safety study, firocoxib was administered orally to healthy juvenile (... 3 weeks of age) Beagle dogs at 5, 15, and 25 mg/kg (1, 3, and 5 times the recommended total daily dose) for 180 days. At the indicated (1X) dose of 5 mg/kg, on histopathologic examination, three out of six dogs had minimal periportal hepatic fatty change. On histopathologic examination, one control, one 1X, and two 5X dogs had diffuse slight hepatic fatty change. These animals showed no clinical signs and had no liver enzyme elevations. In the 3X dose group, one dog was euthanized because of poor clinical condition (Day 63). This dog also had a mildly decreased serum albumin. At study completion, out of five surviving and clinically normal 3X dogs, three had minimal periportal hepatic fatty change. Of twelve dogs in the 5X dose group, one died (Day 82) and three moribund dogs were euthanized (Days 38, 78, and 79) because of anorexia, poor weight gain, depression, and in one dog, vomiting. One of the euthanized dogs had ingested a rope toy. Two of these 5X dogs had mildly elevated liver enzymes. At necropsy all five of the dogs that died or were euthanized had moderate periportal or severe panzonal hepatic fatty change, two had duodenal ulceration, and two had pancreatic edema. Of two other clinically normal 5X dogs (out of ... euthanized as comparators to the clinically affected dogs), one had slight and ... had moderate periportal hepatic fatty change. Drug treatment was discontinued for four dogs in the 5X group. These dogs survived the remaining ... weeks of the study. On average, the dogs in the 3X and 5X dose groups did not gain as much weight as control dogs. Rate of weight gain was measured (instead of weight loss) because these were young growing dogs. Thalamic vacuolation was seen in three of six dogs in the 3X dose group, five of twelve dogs in the 5X dose group, and to a lesser degree in two unmedicated controls. Diarrhea was seen in all dose groups, including unmedicated controls.

In a separate dose tolerance safety study involving a total of six dogs (two control dogs and four treated dogs), firocoxib was administered to four healthy adult Beagle dogs at 50 mg/kg (ten times the recommended daily dose) for twenty-two days. All dogs survived to the end of the study. Three of the four treated dogs developed small intestinal erosion or ulceration. Treated dogs that developed small intestinal erosion or ulceration had a higher incidence of vomiting, diarrhea, and decreased food consumption than control dogs. One of these dogs had severe duodenal ulceration, with hepatic fatty change and associated vomiting, diarrhea, anorexia, weight loss, ketonuria, and mild elevations in AST and ALT. All four treated dogs exhibited progressively decreasing serum albumin that, with the exception of one dog that developed hypoalbuminemia, remained within normal range. Mild weight loss also occurred in the treated group. One of the two control dogs and three of the four treated dogs exhibited transient increases in ALP that remained within normal range.

Storage Store at room temperature between 59°–86° F (15°–30° C). Brief periods up to 104° F (40° C) are permitted.

To Request a Material Safety Data Sheet (MSDS), call 1-866-638-2226.

How Supplied PREVICOX™ is available as round, beige to tan, half-scored tablets in two strengths, containing 57 mg or 227 mg firocoxib. Each tablet strength is supplied in 10 count and 30 count blister packages and 60 count bottles.

1. Willoughby DA, Moore AR and Colville Nash PR. COX-1, COX-2, and COX-3 and the future treatment of chronic inflammatory disease. *Lancet* 2000 355 646–648
2. Smith, *et al*., Pharmacological Analysis of Cyclo-oxygenase-1 in Inflammation. *Proc. Natl Acad Sci USA, Pharmacology* 1998, 95 13313-13318
3. Jones CJ and Budsberg SC. Physiologic characteristics and clinical importance of the cyclooxygenase isoforms in dogs and cats. *JAVMA* 2000 217(5) 721-729
4. Zhang, *et al*., Inhibition of Cyclo-oxygenase-2 Rapidly Reverses Inflammatory Hyperalgesia and Prostaglandin E_2 Production. *JPET* 1997 283 1069-1075
5. Jones and Budsberg pp 721-729
6. Zhang et al pp 1069-1075
7. Chandrasekharan NV, Dai H, et al. COX-3, a cyclooxygenase-1 variant inhibited by acetaminophen and other analgesic/antipyretic drugs: Cloning, structure and expression. *Proc Natl Acad Sci USA*, 2002,99(21) 13926-13931
8. Data on file

Manufactured for: Merial Limited
3239 Satellite Blvd
Duluth, GA 30096-4640, U.S.A.
1-866-638-2226

U.S. Patent Nos 5,981,576, 6,541,646 and 6,677,37...

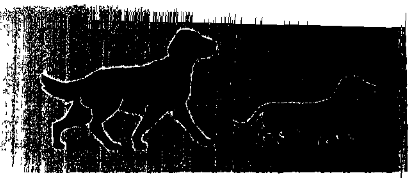
NADA 141-230, Approved by FDA

MERIAL

50C 1727 00
Rev 03 2004

6"W x 16" FRONT

PREVICOX



Dog Owners about ... (...xib) Chewable Tablets

...osteoarthritis pain and inflammation in your dog.

...should read this information before you start giving your dog PREVICOX ... provided only as a summary and does not take the place of instructions ... this information or you want to know more about PREVICOX

What is PREVICOX?

... (NSAID) used to control pain and inflammation due to osteoarthritis in ... cartilage and other parts of the joints that may result in the following

- ...
- ...
- ... or run, or difficulty in performing these activities)
- ...

What kind of results ... is on PREVICOX for osteoarthritis?

... and inflammation and improve your dog's mobility

- ... dramatic
- ...
- ... pain and inflammation may return

Which dogs should ...

Your dog should not ...

- ... PREVICOX
- ... or itchy skin) to aspirin or other NSAIDs
- ...
- ...

PREVICOX should on...

People should not take P... ...ations out of the reach of children. Call your physician immediately if you accidentally take PREVICOX

What to tell/ask your veterinarian ... PREVICOX

Talk to your veterinarian about:

- The signs of osteoarthritis ... as limping or stiffness
- The importance of weight ... hritis
- What tests might be done ...
- How often your dog may ... an
- *The risks and benefits* ... actions, including death, have been associated with PREVICOX administration at doses above the re... ...ven months of age

Tell your veterinarian if your do... ... problems

- Any side effects from tak... ...s aspirin
- Any digestive upset (vomiting ...
- Any kidney disease
- *Any liver disease*

Tell your veterinarian about:

- Any other medical problems ... or has had in the past
- *All medicines that you are* ... luding those you can get without a prescription and any dietary supplements

Tell your veterinarian if your dog:

- *Is pregnant, nursing or* ...

How to give PREVICOX to your dog

PREVICOX should be given ac... ...ctions. Do not change the way you give PREVICOX to your dog without first speaking with your veterinarian. ... amount of PREVICOX is right for your dog and for how long it should be given. Most dogs will take PREVICOX ... , or you can place the tablet in your dog's mouth. *PREVICOX may be given with or without food*

What are the possible side eff... ...ccur in my dog during PREVICOX therapy?

PREVICOX, like other NSAIDS, may cau... ...us side effects associated with *NSAID therapy in dogs can occur with or without* warning, and, in rare situations, result in de... ...ion *side effects associated with PREVICOX* therapy involve the digestive tract (vomiting and *decreased food consumption*) ... ...ems have also been reported with NSAIDs. Look for the following side effects *that may indicate your dog is havi*... ...may have another medical problem

- Decrease or increase in appetite
- *Vomiting*
- Change in bowel movements (such as ... or bloody stools)
- Change in behavior (such as dec... ...vel, incoordination, *seizure, or aggression*)
- Yellowing of gums, *skin, or whites of th*...
- Change in drinking habits (freque...
- Change in urination habits (frequenc...
- Change in skin (redness, sca...
- *Unexpected weight loss*

It is important to stop therapy and contact ... ...ediately *if you think your dog has a medical problem* or side effect while taking PREVICOX tablets. *If you have additional qu...* ... *side effects*, talk with your veterinarian or call 1-866-638-2226

Can PREVICOX be given with ... ...ons?

PREVICOX should not be given with other ... ...*spirin, carprofen, etodolac*, deracoxib, meloxicam, or tepoxalin) or corticosteroids (for *example, prednisone, cortisone, dexam*... ...one)

Tell your veterinarian about all medications ... ...ur dog in the past, and any medications you are *planning to give with* PREVICOX tablets. This should include other medicines ... ...*thout a prescription or any* dietary supplements. Your veterinarian may want to check that *all of your dog's medicines* ...

What do I do in case my dog ... ...than the prescribed amount of PREVICOX?

Consult your veterinarian immediately ... *the prescribed amount of* PREVICOX

What else should I know about PREVICOX?

- This sheet provides a summary of information ... PREVICOX *tablets. If you have any questions* or concerns about PREVICOX or *osteoarthritis pain, talk with your veterinarian*
- As with all prescribed medicines, PREVICOX tablets ... only be given to the dog for which they were prescribed. They should be given to your dog only for the condition for which they were ... ...ed, at the prescribed dose
- It is important to periodically discuss your dog's ... PREVICOX *tablets*. Your veterinarian will determine if your dog is responding as *expected and if your dog should continue receiving* PREVICOX tablets

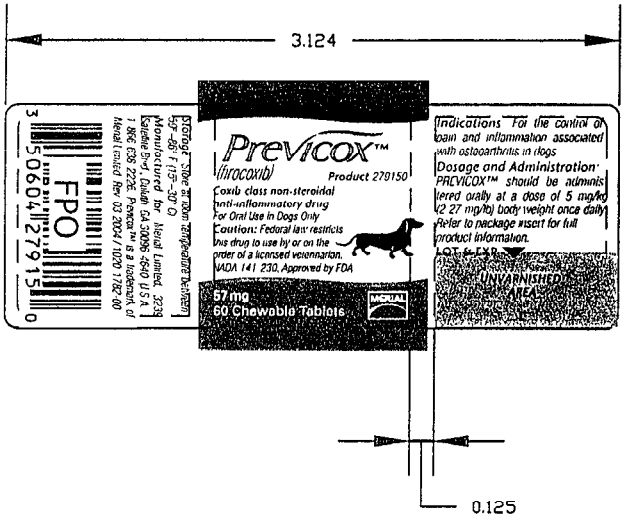
For technical assistance or to report suspected adverse reactions, call *1-866-638-2226.*

NADA 141-230, Approved by FDA

1050-1727-00
Rev 03 2004

MERIAL

6"W x 16"H BACK


3.124
Previcox™
(firocoxib)
Product 279150
Coxib class non-steroidal anti-inflammatory drug
For Oral Use in Dogs Only
Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian.
NADA 141-230, Approved by FDA
57mg
60 Chewable Tablets
Indications: For the control of pain and inflammation associated with osteoarthritis in dogs
Dosage and Administration:
PREVICOX™ should be administered orally at a dose of 5 mg/kg (2.27 mg/lb) body weight once daily.
Refer to package insert for full product information.
LOT & EXP
UNVARNISHED AREA
Storage: Store at 20-25°C (68-77°F); [15-30°C]
Manufactured for Merial Limited, 3239 Satellite Blvd., Duluth, GA 30096-4640 U.S.A.
1-866-638-2226. Previcox™ is a trademark of Merial Limited. Rev. 03 2004 / 1020 1782-00
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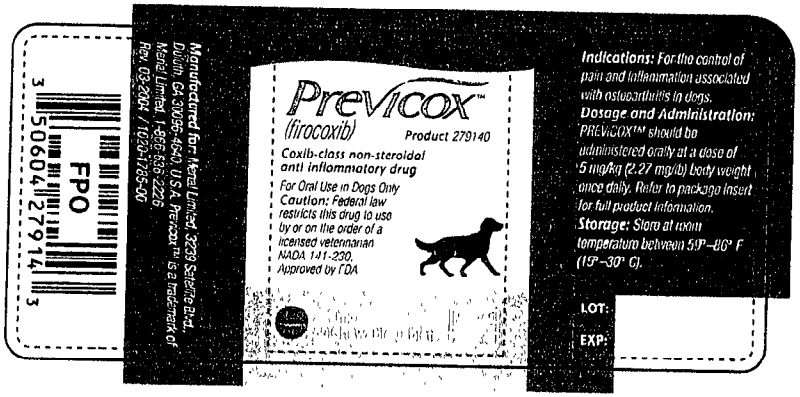
0.125


PREVICOX™
(firocoxib)
Product 279140
Coxib-class non-steroidal anti inflammatory drug
For Oral Use in Dogs Only
Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian
NADA 141-230, Approved by FDA
Indications: For the control of pain and inflammation associated with osteoarthritis in dogs.
Dosage and Administration: PREVICOX™ should be administered orally at a dose of 5 mg/kg (2.27 mg/lb) body weight once daily. Refer to package insert for full product information.
Storage: Store at room temperature between 59°–86° F (15°–30° C).
LOT:
EXP:
Manufactured for: Merial Limited, 3239 Satellite Blvd, Duluth, GA 30096-4640, U.S.A. Previcox™ is a trademark of Merial Limited. 1-866-536-2226
Rev. 03-2004 / 1020-1765-00
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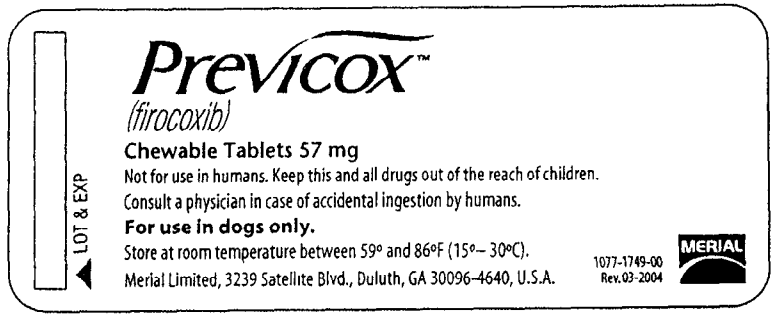
Previcox™
(firocoxib)
Chewable Tablets 57 mg
Not for use in humans. Keep this and all drugs out of the reach of children.
Consult a physician in case of accidental ingestion by humans.
For use in dogs only.
Store at room temperature between 59° and 86°F (15°– 30°C).
Merial Limited, 3239 Satellite Blvd., Duluth, GA 30096-4640, U.S.A.
1077-1749-00
Rev.03-2004
MERIAL
LOT & EXP

Previcox™
(firocoxib)

57 mg
30 Chewable Tablets

Previcox™
(firocoxib)

Product 279120

Indications: For the control of pain and inflammation associated with osteoarthritis in dogs.

Dosage and Administration: PREVICOX™ should be administered orally at a dose of 5 mg/kg (2.27 mg/lb) body weight once daily. Refer to package insert for full product information.

Warnings: Not for use in humans. Keep this and all medications out of the reach of children. Consult a physician in case of accidental ingestion by humans. For use in dogs only.

Storage: Store at room temperature between 59°–86° F (15°–30° C). Brief periods up to 104° F (40° C) are permitted.

Manufactured for:
Merial Limited, 3239 Satellite Blvd., Duluth, GA 30096-4640, U.S.A.
1-866-638-2226

1030-1783-00
Rev. 03-2004

MERIAL

57 mg
30 Chewable Tablets

Previcox™
(firocoxib)

57 mg | 30 Chewable Tablets

Coxib-class non-steroidal anti-inflammatory drug
For Oral Use in Dogs Only Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian.
NADA 141-230, Approved by FDA

Previcox™
(firocoxib)

Lot & Exp

57 mg
30 Chewable Tablets

PATHEON GMP CODE

FPO

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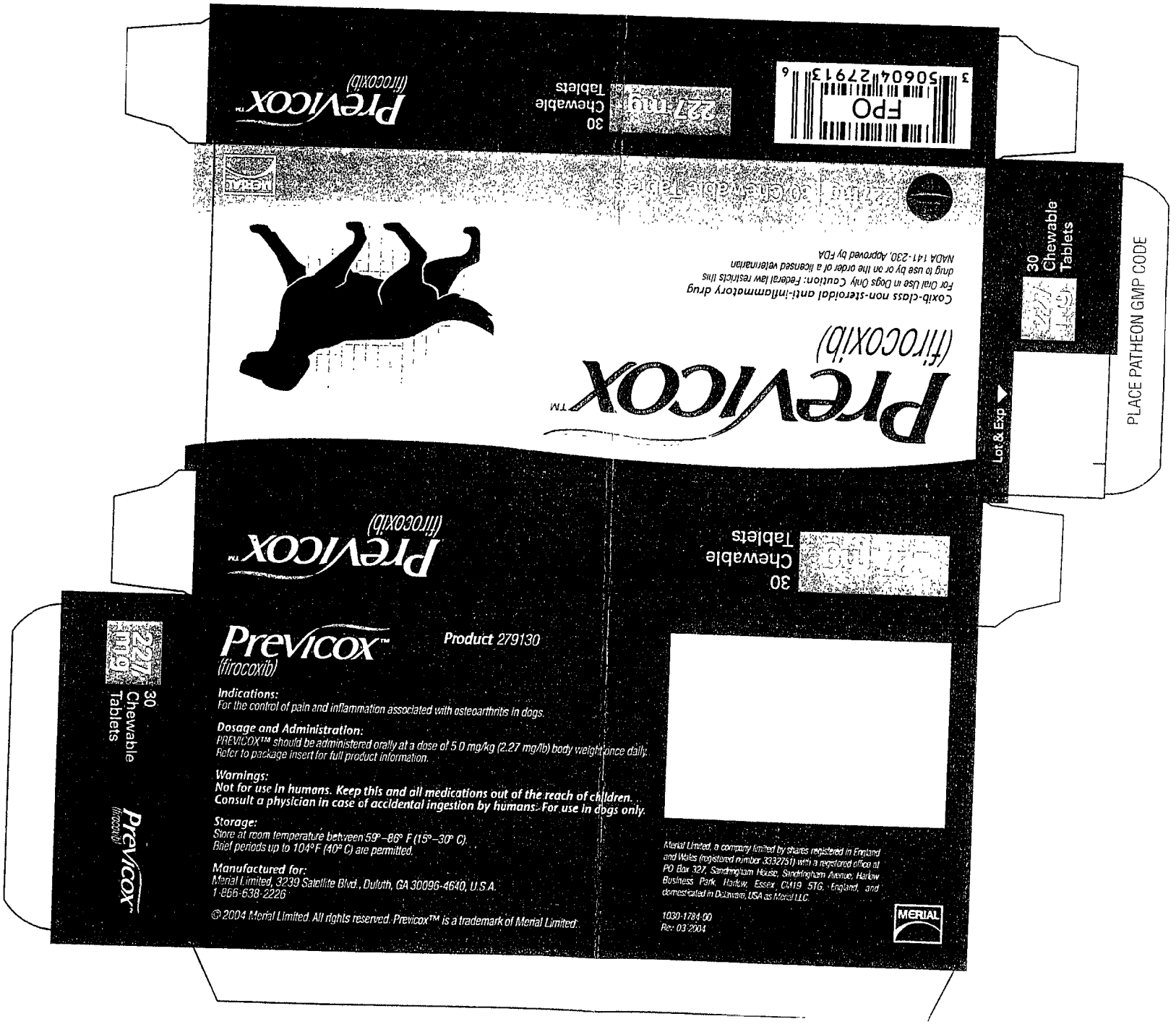
Previcox™
(firocoxib)
Product 279130
Indications:
For the control of pain and inflammation associated with osteoarthritis in dogs.
Dosage and Administration:
PREVICOX™ should be administered orally at a dose of 5.0 mg/kg (2.27 mg/lb) body weight once daily.
Refer to package insert for full product information.
Warnings:
Not for use in humans. Keep this and all medications out of the reach of children.
Consult a physician in case of accidental ingestion by humans. For use in dogs only.
Storage:
Store at room temperature between 59°–86° F (15°–30° C).
Brief periods up to 104°F (40° C) are permitted.
Manufactured for:
Merial Limited, 3239 Satellite Blvd., Duluth, GA 30096-4640, U.S.A.
1-866-638-2226
© 2004 Merial Limited. All rights reserved. Previcox™ is a trademark of Merial Limited.
227 mg
30 Chewable Tablets
Coxib-class non-steroidal anti-inflammatory drug
For Oral Use in Dogs Only. Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian
NADA 141-230, Approved by FDA
Merial Limited, a company limited by shares registered in England and Wales (registered number 3332751) with a registered office at PO Box 327, Sandringham House, Sandringham Avenue, Harlow Business Park, Harlow, Essex, CM19 5TG, England, and domesticated in Delaware, USA as Merial LLC.
1030-1784-00
Rev: 03/2004
MERIAL
Lot & Exp
PLACE PATHEON GMP CODE
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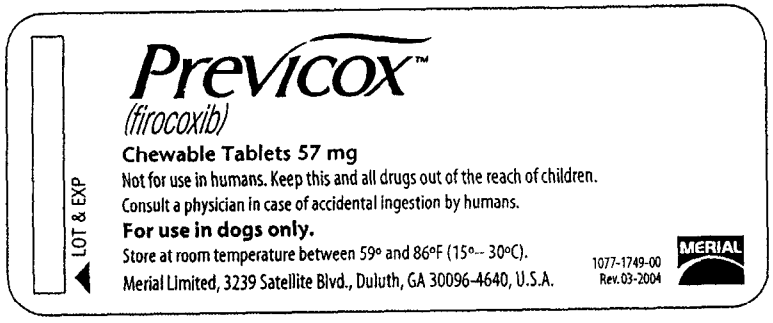
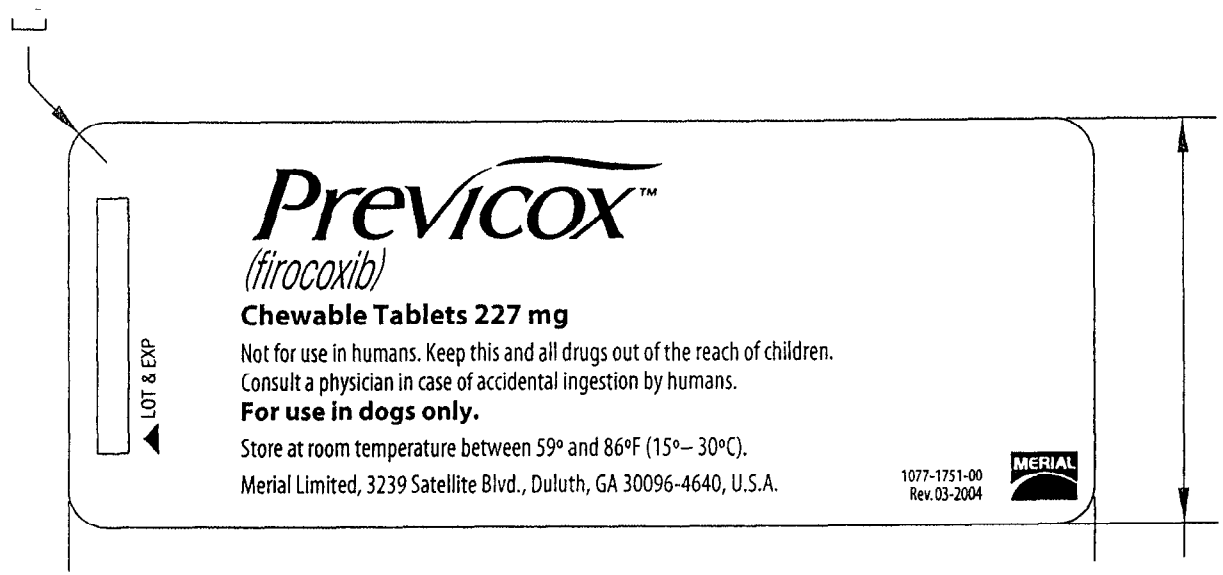
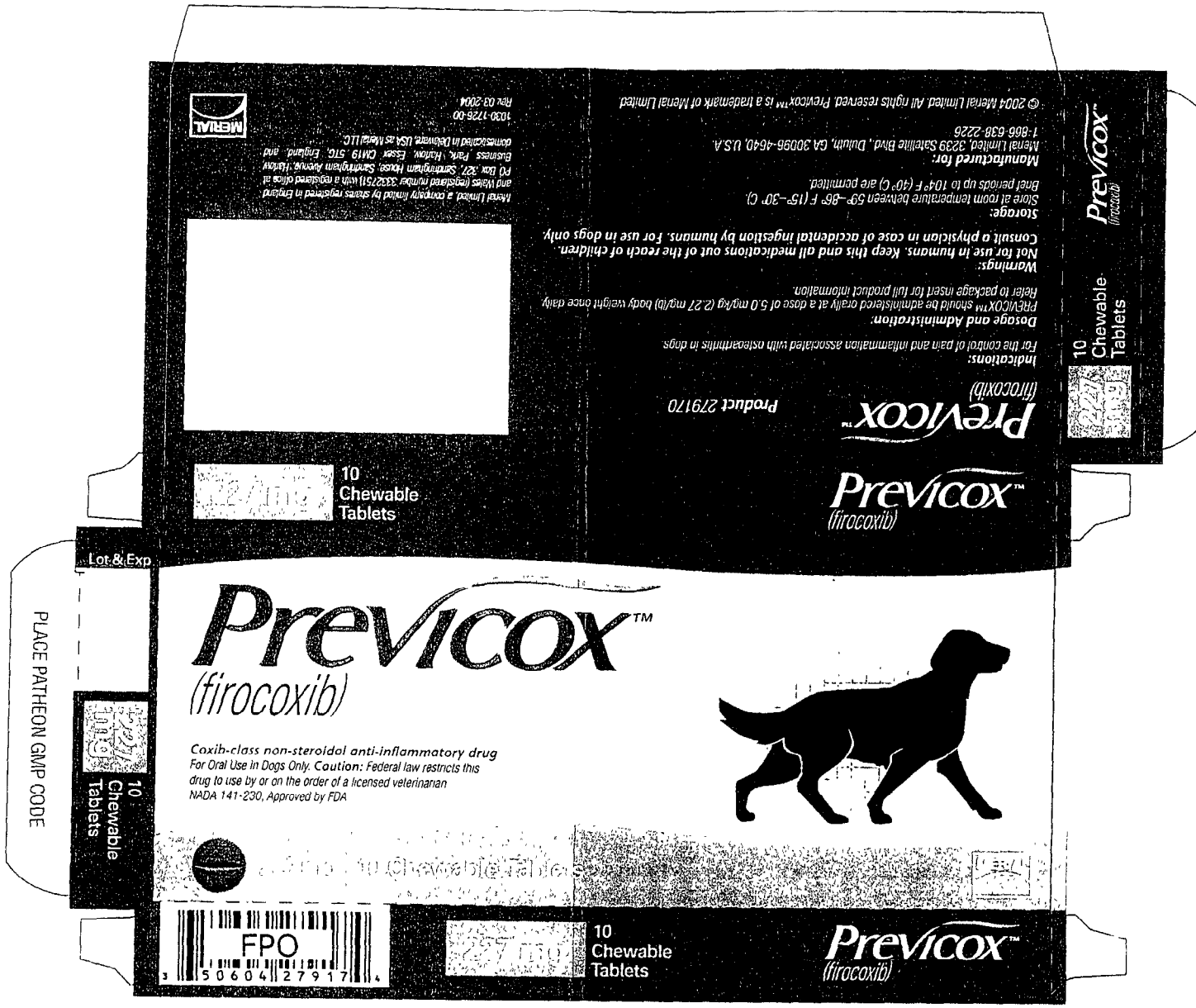

Previcox™
(firocoxib)
Chewable Tablets 57 mg
Not for use in humans. Keep this and all drugs out of the reach of children.
Consult a physician in case of accidental ingestion by humans.
For use in dogs only.
Store at room temperature between 59° and 86°F (15°-- 30°C).
Merial Limited, 3239 Satellite Blvd., Duluth, GA 30096-4640, U.S.A.
1077-1749-00
Rev.03-2004
MERIAL
LOT & EXP


LOT & EXP
Previcox™
(firocoxib)
Chewable Tablets 227 mg
Not for use in humans. Keep this and all drugs out of the reach of children.
Consult a physician in case of accidental ingestion by humans.
For use in dogs only.
Store at room temperature between 59° and 86°F (15°– 30°C).
Merial Limited, 3239 Satellite Blvd., Duluth, GA 30096-4640, U.S.A.
1077-1751-00
Rev. 03-2004
MERIAL

57 mg
10 Chewable Tablets
Previcox™
(firocoxib)
Lot & Exp
PATHEON CMP CODE
Previcox™
(firocoxib)
Coxib-class non-steroidal anti-inflammatory drug
For Oral Use in Dogs Only Caution Federal law restricts this drug
to use by or on the order of a licensed veterinarian
NADA 141-230, Approved by FDA
57 mg | 10 Chewable Tablets
MERIAL
FPO
3 50604 27916 7
57 mg
10 Chewable Tablets
Previcox™
(firocoxib)
Product 279160
Indications: For the control of pain and inflammation associated with osteoarthritis in dogs
Dosage and Administration: PREVICOX™ should be administered orally at a dose of 5 mg/kg (2.27 mg/lb) body weight once daily. Refer to package insert for full product information.
Warnings: Not for use in humans. Keep this and all medications out of the reach of children. Consult a physician in case of accidental ingestion by humans.
For use in dogs only.
Storage: Store at room temperature between 59°–86° F (15°–30° C). Brief periods up to 104° F (40° C) are permitted.
Manufactured for:
Merial Limited, 3239 Satellite Blvd., Duluth, GA 30096-4640, U.S.A.
1-866-638-2226
© 2004 Merial Limited. All rights reserved. Previcox™ is a trademark of Merial Limited
Merial Limited, a company fented by shares registered in England
and Wales (registered number 3332751) with a registered office at
Merial, 3rd, Sandringham House, Sandringham Avenue, Harlow
Business Park, Harlow, Essex, CM19 5TG, England, and
manufactured in Germany, USA as Merial LLC.
1030-1725-00
Rev 03-2004
MERIAL
57 mg
10 Chewable Tablets
Previcox™
(firocoxib)


PLACE PATHEON GMP CODE
Lot & Exp
10 Chewable Tablets
Previcox™
(firocoxib)
Coxib-class non-steroidal anti-inflammatory drug
For Oral Use in Dogs Only. Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian
NADA 141-230, Approved by FDA
FPO
10 Chewable Tablets
Previcox™ (firocoxib)
Product 279170
Indications:
For the control of pain and inflammation associated with osteoarthritis in dogs.
Dosage and Administration:
PREVICOX™ should be administered orally at a dose of 5.0 mg/kg (2.27 mg/lb) body weight once daily
Refer to package insert for full product information.
Warnings:
Not for use in humans. Keep this and all medications out of the reach of children.
Consult a physician in case of accidental ingestion by humans. For use in dogs only.
Storage:
Store at room temperature between 59°–86° F (15°–30° C).
Brief periods up to 104° F (40° C) are permitted.
Manufactured for:
Merial Limited, 3239 Satellite Blvd., Duluth, GA 30096-4640, U.S.A.
1-866-638-2226
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Merial Limited, a company formed by shares registered in England and Wales (registered number 3332751) with a registered office at PO Box 327, Sandringham House, Sandringham Avenue, Harlow Business Park, Harlow, Essex, CM19 5TG, England, and domesticated in Delaware, USA as Merial LLC.
1030-1726-00
Rev. 03-2004
MERIAL


Previcox™
(firocoxib) 57 mg Chewable Tablets
MERIAL
1032-1729-00
Rev. 03-2004
Previcox™
(firocoxib) 57 mg Chewable Tablets
MERIAL
Previcox™
(firocoxib) 57 mg Chewable Tablets
MERIAL
57 mg Chewable Tablets
MERIAL

8.5625


Previcox™
(firocoxib) 57 mg Chewable Tablets
MERIAL
1032-1729-00
Rev. 03-2004
Previcox™
(firocoxib) 57 mg Chewable Tablets
MERIAL
Previcox™
(firocoxib) 57 mg Chewable Tablets
MERIAL
57 mg Chewable Tablets
MERIAL

8.5625


Previcox™
(firocoxib) 227 mg Chewable Tablets
MERIAL
1032-1731-00
Rev. 03-2004
Previcox™
(firocoxib) 227 mg Chewable Tablets
MERIAL
Previcox™
(firocoxib) 227 mg Chewable Tablets
MERIAL


Previcox™
(firocoxib) 227 mg Chewable Tablets
MERIAL
1032-1731-00
Rev. 03-2004
Previcox™
(firocoxib) 227 mg Chewable Tablets
MERIAL
Previcox™
(firocoxib) 227 mg Chewable Tablets
MERIAL

9¾

PREVICOX™
(firocoxib) 57mg Chewable Tablets

Contains:
24 Bottles of 60 Chewable Tablets (Item 279150)

Store At 59° – 86°F (15° – 30° C)
CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

Qty: 0012 ITEM NO.: 279150 LOTNO.: XXX999

0012279160XXX999

LOT NO.:
XXX999
EXP. DATE:
99 9999

NDC Code

CONTENTS MADE IN CANADA
Manufactured For:
MERIAL LIMITED
DULUTH, GA 30096 U.S.A.

1025-1828-00
Rev. 03-2004

PREVICOX™
(firocoxib) 227mg Chewable Tablets

Contains:
24 Bottles of 60 Chewable Tablets (Item 279140)

Store At 59° – 86°F (15° – 30° C)
CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

Qty: 0012 ITEM NO.: 279140 LOTNO.: XXX999

0012279160XXX999

LOT NO.:
XXX999
EXP. DATE:
99 9999

NDC Code

CONTENTS MADE IN CANADA
Manufactured For:
MERIAL LIMITED
DULUTH, GA 30096 U.S.A.

1025-1829-00
Rev. 03-2004

PREVICOX™
(firocoxib) 57mg Chewable Tablets

Contains:
12 Trays of 6 X 30 Chewable Tablets (Item 279120)

Store At 59° – 86°F (15° – 30° C)
CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

Qty: 0012 ITEM NO.: 279120 LOTNO.: XXX999

0012279160XXX999

LOT NO.:
XXX999
EXP. DATE:
99 9999

NDC Code

CONTENTS MADE IN CANADA
Manufactured For:
MERIAL LIMITED
DULUTH, GA 30096 U.S.A.

1025-1826-00
Rev 03-2004

PREVICOX™
(firocoxib) 227mg Chewable Tablets

Contains:

12 Trays of 6 X 30 Chewable Tablets (Item 279130)

Store At 59° – 86°F (15° – 30° C)
CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

Qty: 0012 ITEM NO.: 279130 LOTNO.: XXX999

FPO

0012279160XXX999

LOT NO.:
XXX999
EXP. DATE:
99 9999

NDC Code

FPO

N 3 50604 99999 7

CONTENTS MADE IN CANADA
Manufactured For:
MERIAL LIMITED
DULUTH, GA 30096 U.S.A.

1025-1827-00
Rev. 03-2004

PREVICOX™
(firocoxib) 57mg Chewable Tablets

Contains:

12 Trays of 10 X 10 Chewable Tablets (Item 279160)

Store At 59° – 86°F (15° – 30° C)
CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

Qty: 0012 ITEM NO.: 279160 LOTNO.: XXX999

0012279160XXX999

LOT NO.:
XXX999
EXP. DATE:
99 9999

NDC Code

CONTENTS MADE IN CANADA
Manufactured For:
MERIAL LIMITED
DULUTH, GA 30096 U.S.A.

1025-1824-00
Rev. 03-2004

PREVICOX™
(firocoxib) 227mg Chewable Tablets

Contains:
12 Trays of 10 X 10 Chewable Tablets (Item 279170)

Store At 59° – 86°F (15° – 30° C)
CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

Qty: 0012 ITEM NO.: 279170 LOTNO.: XXX999

0012279160XXX999

LOT NO.:
XXX999
EXP. DATE:
99 9999

NDC Code

CONTENTS MADE IN CANADA
Manufactured For:
MERIAL LIMITED
DULUTH, GA 30096 U.S.A.

1025-1825-00
Rev. 03-2004